least 25% daily replacement continuously for more than one day.--

REMARKS

Claims 6-12 and 38-47 are active in the present application. Support for Claim 47 is found in Claim 1 and the specification as filed. Support for Claim 47 is found on pages 17-18 of the specification The specification is amended for clarity. No new matter is believed to have been added by these amendments. Favorable reconsideration is respectfully requested.

Applicants wish to thank Examiner Tung for the courteous discussion held with the undersigned Applicants' representative on September 6, 2000. The substance of this discussion is expanded upon in the remarks made below.

The present invention applies to the culture of lineage committed human cells based on the discovery that by replacing liquid culture media in a lineage committed human cell culture without substantially changing the cell density, it is possible to obtain cells having an enhanced biological function.

The rejection of Claims 1-6, 9-14 and 33-45 under 35 U.S.C. §102(b) over Kraus is respectfully traversed.

Kraus discloses a method of expanding a selective population of cells by growing the cells in culture and specific selection agents to bind to specific cell types to allow for the selective expansion (see Claim 1 and columns 1-3 of Kraus). It is the specific selection agent which is critical to the invention disclosed in Kraus. However, Kraus do not disclose the present method of obtaining **lineage committed human cells** having **enhanced biological function** as recited in Claim 1.

Such biological functions are discussed on pages 11-12 of the present specification:

> Examples of biological function include secretion of substances (such as cytokines, hormones, antibodies, etc.), cell-

cell communication, receptor expression on the cell surface, cytolysis, antigen presentation, antigen processing, ability to home *in vivo* to sites for function, ability to proliferate leading to development/regeneration of tissue similar to naturally occurring structure/function.

The claimed lineage committed human cells are defined in the specification on page 6 through page 7 of the specification: "The lineage committed human cell used in accordance with the present invention are cells which are differentiated to at least a point where they are programmed to develop into a specific of cell. These cells are not necessarily terminally differentiated. On page 7, lines 4-5 the specification states: "In one embodiment, the lineage committed cells are more differentiated than human stem cells."

The reference does not disclose the culture conditions for culturing such lineage committed cells nor the recognition that in so culturing such cells, one could obtain cells with enhanced biological function. This is particularly true in light of the Kraus disclosure for only expanding a population of stem cells.

It is the lineage committed cells having enhanced biological function which can be advantageously used in a human therapies, e.g., see pages 1-3 of the present specification. Absent some disclosure in Kraus for obtaining lineage committed cells having enhanced biological function, Kraus do not anticipate the present claims. Accordingly, withdrawal of this ground of rejection is respectfully requested.

The rejection of Claims 1, 7 and 8 under 35 U.S.C. §103(a) over Kraus in view of Schwartz et al is respectfully traversed.

The deficiencies of Kraus are discussed above. Schwartz et al do not remedy these deficiencies because Schwartz et al merely teach a method of expanding a population of hematopoietic stem cells (see column 2, lines 25-29). Thus, the combination of the two references does not suggest in any way a method for obtaining lineage committed cells

having enhanced biological function nor do the references suggest a need for such cells. The only recognized purpose of the methods disclosed (taken separately or together) is to expand the number of cells present in the culture. To this end, the methods disclosed in Kraus and Schwartz et al may be better at producing higher quantities of cells (expansion) but these cells would have a reduced biological activity as compared to the cells cultured in accordance with the present claims.

The references are silent regarding the biological functions or the need to obtain lineage committed cells with enhanced biological function. Contrary to the Examiner's statement on page 3, pre-numbered paragraph 8, clongenic expansion is not the same as proliferative potential which is one of the claimed enhanced biological functions (see Claim 46). Clonogenic expansion is the multiplication of the number of cells present whereas replicative potential means:

> . . . product cells have a greater ability to produce more cells as compared to the cells that were used at the beginning of the culturing. . . the product cells of the present invention have a greater ability to replicate or further differentiate to the desired cell type as compared to the same cells which have been cultured at low densities in a static culture (page 9, lines 15-19)

Thus, in one aspect of such enhanced replicative potential the cells obtained in accordance with the present method are more capable of replication even after they are removed from the culture, e.g., upon transplantation into a patient, compared to cells which are simply expanded (as in the references). Neither reference discloses or suggests such a potential.

The enhanced biological functions for various cell types is presented in the specification. For example, $CD8^+$ cells cultured in accordance with the claimed method are described in Example 2, pages 24-26: "These results demonstrate the benefit of continuous perfusion enhancing the replicative potential of human $CD8^+$ cells (page 25, lines 12-14) . . .

The data indicates that T-cells derived in the CPS are fully responsive to stimulation through the TCR-CD3 complex and they produce higher levels of particular cytokines on a per cell basis than T-cells produced in T-flask" (Page 25, lines 19-21). Additional evidence of the claimed method is shown in Example 3 for human dendritic cells, and Example 4 for chondrocytes.

The references neither suggest such results nor provide any expectation for the enhanced biological activity obtained with the present method. Without a suggestion or recognition of the enhanced biological activity of the lineage committed cells, the references certainly do not provide a suggestion for a **method for obtaining** lineage committed cells having enhanced biological function. Thus, the present claims are not obvious in view of Kraus and Schwartz and withdrawal of this ground of rejection is respectfully requested.

Applicants submit that the present application is now in condition for allowance. Early notification of such is earnestly solicited.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.

Jean-Paul Lavalleye, Ph.D.
Registration No. 31,451

Daniel J. Pereira, Ph.D.
Registration No. 45,518

22850
(703) 413-3000
Fax #: (703) 413-2220
JPL:DJP\cct

I:\user\DJPER\2000\12.Dec-00\42920048-am.wpd